REMARKS

At the outset, the Applicant and the Applicant's undersigned attorney appreciate the Examiner's willingness to discuss the present application in a personal interview conducted on May 17, 2004. During the interview, the previously pending claims were discussed, the present amendments to the claims were discussed, and the differences between the Applicant's presently claimed invention and the disclosures made in the Rhode et al. 6,232,445 patent were discussed. It is the undersigned's recollection that the Examiner indicated that the claim amendments discussed (and reflected in the currently amended claims) put the claims into a condition for allowance.

The Examiner is also thanked for being willing to review and enter this response "after Final."

Claim Rejections Under 35 USC § 112

In the Office Action dated March 9, 2004, the Examiner rejected claims 1, 2, and 5-13 under 35 USC 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Applicant respectfully submits that the claims, as currently amended, particularly point out and distinctly claim the subject matter which applicant regards as the invention. In particular, the Applicant herein has amended the claims to remove the phrase "large scale." As such, the rejection under 35 USC

112, second paragraph has been rendered moot and the Examiner is respectfully urged to withdraw this rejection and pass the claims to an expedient issuance.

Claim Rejections Under 35 USC § 102

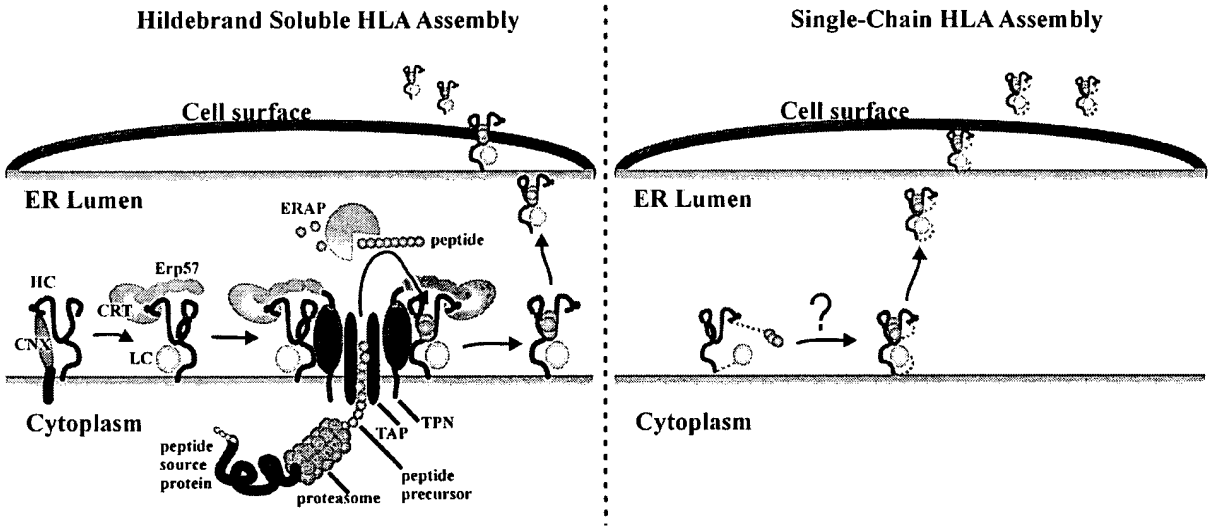
In the Office Action dated March 9, 2004, the Examiner rejected claims 1, 2, and 5-14 under 35 USC 102(e) as being anticipated by U.S. Patent No. 6,232,445 B1 to Rhode et al. (A on form PTO-892).

Applicant respectfully traverses the Examiner's rejection under 35 USC 102(e) on the following grounds.

As background, multiple methods are currently employed to create class I MHC molecules. In the current application, the Applicant describes a method for the creation of soluble class I MHC molecules that is completely different from other known methods. The main difference between prior art molecules and methods and the presently claimed invention is that the presently claimed soluble class I MHC molecules are naturally assembled within the cell to form heterotrimers comprising the recombinantly introduced heavy chain, naturally or endogenously produced light chain (β_2m), and naturally produced and endogenously loaded antigenic peptides. Once properly assembled by the host cell, the Applicant's presently claimed soluble class I MHC molecules are secreted outside of the cell.

Previous technologies have relied on mutagenesis strategies to artificially

link either two components (heavy chain and β_2m) or three components (heavy chain, β_2m, and peptide) using flexible linkers. Utilizing these known technologies, at least the heavy chain and β_2m are translated together as a single polypeptide, and then folded together by the cell to attain their proper conformation. In the event a peptide is attached by a linker, this peptide typically folds "back" into the peptide-binding groove of the heavy chain. These artificial molecules can then be created in a number of cell lines, or can be used to make soluble HLA molecules composed of a single chain. The events that occur within the endoplasmic reticulum to create the folded molecule (including the chaperones involved) are unclear, however it is unlikely that the classical class I pathway is used.



The above figure represents and illustrates the different mechanisms

involved in the production of the presently claimed soluble class I MHC molecules (left panel, entitled "Hildebrand Soluble HLA Assembly") and the single chain soluble class I MHC molecules produced by others and, for example, according to U.S. Patent No. 6,232,445 to Rhode et al.

In the Rhode, et al. '445 patent there is no demonstration that the artificially linked constructs interact with the many intracellular chaperones that are needed for proper endogenous peptide loading. In contrast, the Applicant performed experiments (as outlined in the present specification) that show that Applicant's truncated sHLA class I heavy chain traffics naturally through the cell, complexes with beta-2-microglobulin that is native to the cell, and that this dimer is thereafter loaded with thousands of different endogenous and naturally produced peptides – the same process that takes place within a normal unmanipulated cell. Such trafficking is one of the main components of the Applicant's currently claimed invention -- the modified heavy chain molecule that is recombinantly inserted into the host cell interacts naturally and appropriately with the cell's chaperones (including assembly with native endogenously produced beta-2-microglobulin) and is loaded with natural and endogenously produced peptides. Applicant's methodology involves the removal of a portion of the class I heavy chain; the truncated class I heavy chain maintains its function and traffics through the cell as the native full length version, except that the truncated class I heavy chain is soluble and thus a

secreted molecule that can be harvested.

Another important consideration is the fact that native, endogenously produced beta-2-microglobulin complexes with the recombinantly introduced class I heavy chain. As such, the tri-molecular complex comes together naturally, thereby allowing for the direct comparison and use of the soluble class I MHC molecules so produced. Such naturally trafficked and naturally produced soluble class I MHC molecules are essential to the development of vaccines – any vaccine development strategy utilizing soluble class I MHC molecules requires that the soluble class I MHC molecules appropriately and accurately reflect the actual conditions that exist inside the cell of interest. In the Rhode et al. '445 patent there is no demonstration that the described and claimed artificial single chain class I constructs naturally come together with peptides or chaperones. Without a demonstration that this takes place, there is no assurance that the peptides associated with the artificial single chain class I constructs would also associate with naturally occurring class I complexes, and thus the data describing the resulting peptides is not relevant and can not be used for vaccine or diagnostic design. Simply put, any data derived from molecules produced according to the Rhode et al. methodology would be suspect since it does not characterize the conditions within the cell of interest.

In contrast, the HLA molecules presently disclosed and claimed are *not* single-chain products: rather, only the heavy chains are introduced into a

mammalian cell line. These heavy chains have been engineered by the Applicant to associate with the cell's own naturally produced light chain (β_2m) without the use of any linker. The presently claimed and disclosed soluble class I MHC molecules are specifically engineered to have their transmembrane and cytoplasmic domains removed from the resulting molecule. Follow on experimentation through immunoprecipitation experiments (and other experiments from different labs) have shown that Applicant's presently claimed soluble class I MHC molecules retain their association with the class I MHC cellular loading pathways and chaperones. Therefore, these molecules are naturally assembled as shown in the above-illustrated figure.

It should be once more noted that Applicant's presently claimed molecules utilize the cell's natural source of beta-2-microglobulin. If a virus were to shut down beta-2-microglobulin, then an infected cell would not secrete or present class I MHC molecules on its surface. Such an infected cell transfected with the Applicant's claimed truncated heavy chain molecule would also lose the ability to produce and present such class I MHC molecules. Rhode et al's. methodology would result in the cell producing and secreting class I MHC molecules regardless of whether the cell's class I pathways and chaperones were functioning properly, as Rhode et al's. methods do not utilize the cell's natural pathways to form, traffic, fold, and load the class I MHC molecules with peptides. Thus, the Applicant's presently claimed soluble class

I MHC molecules mirror what happens *in vivo* whereas Rhode et al's. claimed molecules do not represent what happens within an infected cell, and the resulting data would lead to failed vaccine development.

Additionally, since Applicant uses the natural β_2m encoded by the cell line, the Applicant's molecules and methodology can be used to create hybrid molecules consisting of a primate MHC heavy chain (Mamu, for instance) and a human β_2m. This allows the use of standard reagents (such as anti-human β_2m monoclonal antibodies) for detection of the hybrid molecules which would otherwise not be available. Additionally, any polymorphisms in the β_2m of the cell line used for production will also be included in the soluble class I MHC molecules produced according to the Applicant's methodology. In a similar manner, the peptides of the sMHC complexes produced using Applicant's methodology are naturally created and loaded using the endogenous cellular machinery. This is not true for the single-chain molecules produced by the methods of Rhode et al.

Finally, in nature class I MHC molecules associate and dissociate with their light chain and peptides. The strongest binding peptides remain associated, while weaker ones rapidly dissociate. Allowing the three components of the soluble class I MHC molecules to naturally associate/dissociate yields a more natural final product. For instance, β_2m dissociation and reassociation is used to allow peptides to be displaced from the

peptide-binding groove. By flooding the soluble class I molecules with excess β_2m, the Applicant's claimed soluble class I MHC molecules can be used in peptide-binding assays that force peptide replacements.

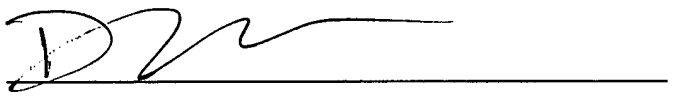
In conclusion, Applicant's soluble class I MHC molecules do not artificially associate the heavy chain with β_2m and peptide, whereas the molecules of Rhode et al. are single chain constructs trafficked artificially through the cell. Thus, the two approaches for producing soluble class I molecules are entirely distinct, each with their own unique advantages, and the Rhode et al. '445 patent does not anticipate nor render obvious the Applicant's currently amended and pending claims. As such, the Examiner is urged to withdraw the rejection and pass the claims to an expedient issuance.

Conclusion

It is respectfully submitted that the claims of this application, as now amended, are in condition for allowance for the reasons stated above. Therefore, it is requested that the Examiner reconsider each and every rejection as applicable to the claims now pending in the application and pass such claims to issue.

This amendment is intended to be a complete response to the Office Action dated March 9, 2004. In the event that any outstanding issues remain that would delay the allowance of this application, the examiner is urged to contact the undersigned to telephonically discuss such outstanding issues.

Respectfully submitted,



Douglas J. Sorocco, Reg. No. 43,145
DUNLAP, CODDING & ROGERS, P.C.
Post Office Box 16370
Oklahoma City, Oklahoma 73113
(405) 607-8600 - Telephone
(405) 607-8686 - Telefax

Attorney for Applicant